Telmisartan Amlodipine besilate

Twynsta®

Boehringer Ingelheim

Angiotensin II Antagonist/Calcium Channel Blocker

Product Description

Telmisartan / amlodipine layered tablets 40/5 mg are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A1. The tablets are for oral administration.

Telmisartan / amlodipine layered tablets 40/10 mg are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A2.

Telmisartan / amlodipine layered tablets 80/5 mg are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A3.

Telmisartan / amlodipine layered tablets 80/10 mg are layered tablets of oval, biconvex shape. The two layers have different colours with the telmisartan layer being white to off- white, the amlodipine layer is blue. The white layer is debossed with the Boehringer Ingelheim company symbol and the code A4.

Formulation

1 tablet contains:

[1,1'-biphenyl]-2-carboxylic acid, 4'-[(1,4'dimethyl-2'-propyl [2,6-bi-1H-benzimidazole]-1'-yl)methyl]
(= telmisartan) 40 or 80 mg

3-ethyl-5-methyl (4RS)-2-[-(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3.5-dicarboxylate
(= amlodipine) 5 or 10 mg, as besilate

Excipients: colloidal anhydrous silica, FD&C blue No 1 aluminium lake (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol

Indications/Usage

Treatment of essential hypertension.

Replacement Therapy

Patients receiving telmisartan and amlodipine besilate from separate tablets may instead receive Telmisartan + Amlodipine besilate (TWYNSTA) containing the same component doses.

Add on therapy

Telmisartan + Amlodipine besilate (TWYNSTA) is indicated in patients whose blood pressure is not adequately controlled on telmisartan or amlodipine monotherapy.

Initial therapy

Telmisartan + Amlodipine besilate (TWYNSTA) may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of Telmisartan + Amlodipine besilate (TWYNSTA) as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

Dosage and Administration

Dosage

Adults

Telmisartan + Amlodipine besilate (TWYNSTA) should be taken once daily.

Replacement therapy

Patients receiving telmisartan and amlodipine besilate from separate tablets can instead receive Telmisartan + Amlodipine besilate (TWYNSTA) containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance.

Add on therapy

Telmisartan + Amlodipine besilate (TWYNSTA) may be administered in patients whose blood pressure is not adequately controlled with amlodipine or telmisartan alone.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Telmisartan + Amlodipine besilate (TWYNSTA) 40/5mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Initial therapy

A patient may be initiated on Telmisartan + Amlodipine besilate (TWYNSTA) if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of Telmisartan + Amlodipine besilate (TWYNSTA) is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on Telmisartan + Amlodipine besilate (TWYNSTA) 80/5 mg once daily.

If additional blood pressure lowering is needed after at least 2 weeks of therapy, the dose may be titrated up to a maximum of 80/10 mg once daily.

Telmisartan + Amlodipine besilate (TWYNSTA) can be administered with other antihypertensive drugs.

Special populations

Geriatric patients

No dose adjustment is necessary for geriatric patients.
Normal amlodipine dosage regimens are recommended in the elderly, but increase of dosage should take place with care (see sections Special warnings and precautions, and Pharmacokinetics).

Paediatric patients

Telmisartan + Amlodipine besilate (TWYNSTA) is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Renal impairment

No posology adjustment is required for patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

Hepatic impairment

In patients with mild to moderate hepatic impairment Telmisartan + Amlodipine besilate (TWYNSTA) should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section Contraindications).

Method of Administration

Telmisartan + Amlodipine besilate (TWYNSTA) tablets are for once-daily oral administration and should be swallowed whole with liquid. Telmisartan + Amlodipine (TWYNSTA) can be taken with or without food.

HANDLING INSTRUCTIONS

Due to the hygroscopic property of the tablets they should be taken out of the sealed blister shortly before administration.

Contraindications

- Hypersensitivity to the active substances, or to any of the excipients.
- Hypersensitivity to dihydropyridine derivatives
- Second and third trimesters of pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction
- The concomitant use of Telmisartan + Amlodipine besilate (TWYNSTA) with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²)

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see section Special warnings and precautions) the use of the product is contraindicated.

Special Warnings and Precautions

Pregnancy

Angiotensin II receptor blockers should not be initiated during pregnancy.
Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and if appropriate, alternative therapy should be started.

Hyperkalaemia
During treatment with medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with telmisartan.

Volume and/or sodium depleted patients
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Telmisartan + Amlodipine besilate (TWYNSTA).

Hepatic impairment
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance.
The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose.
Telmisartan + Amlodipine besilate (TWYNSTA) should therefore be used with caution in these patients.

Renovascular hypertension
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplant
When Telmisartan + Amlodipine besilate (TWYNSTA) is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan + Amlodipine besilate (TWYNSTA) in patients with a recent kidney transplant. Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

Dual blockade of the renin-angiotensin-aldosterone system
As a consequence of inhibiting the renin-angiotensin-aldosterone system changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Telmisartan + Amlodipine besilate (TWYNSTA) can be administered with other antihypertensive drugs, however dual blockade of the renin-angiotensin- aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor blocker) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function (see section Contraindications).

Other conditions with stimulation of the renin-angiotensin-aldosterone system
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction
There are no data to support the use of Telmisartan + Amlodipine besilate (TWYNSTA) in unstable angina pectoris and during or within one month of a myocardial infarction.

Patients with cardiac failure
In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution.
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Sodium
Telmisartan + Amlodipine besilate (TWYNSTA) tablets 40/5 mg, 40/10 mg, 80/5 mg and 80/10 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Sorbitol
Telmisartan + Amlodipine besilate (TWYNSTA) tablets 40/5 mg and 40/10 mg contain 168.64 mg sorbitol in each tablet.

Telmisartan + Amlodipine besilate (TWYNSTA) tablets 80/5 mg and 80/10 mg contain 337.28 mg sorbitol in each tablet.
Sorbitol is a source of fructose. Telmisartan + Amlodipine besilate (TWYNSTA) tablets 80/5mg and 80/10 mg are not recommended for use in patients with hereditary fructose intolerance (HFI).

Diabetes mellitus
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with Telmisartan + Amlodipine besilate (TWYNSTA).

Geriatric patients
The increase of the amlodipine dosage should take place with care in the geriatric patients (see sections Dosage and Administration and Pharmacokinetics)

Ethnic differences
Telmisartan + Amlodipine besilate (TWYNSTA) was effective when treating black patients (usually a low-renin population).

Ischaemic heart disease
As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

USE IN SPECIFIC POPULATIONS

Pregnancy, Lactation and Fertility
The effects of Telmisartan + Amlodipine besilate (TWYNSTA) during pregnancy and lactation are not known. Effects related to the mono components are described below.

Pregnancy
Telmisartan:
The use of angiotensin II receptor blockers is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

The use of angiotensin II receptor blockers is contraindicated during the second and third trimester of pregnancy. Angiotensin II receptor blockers exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II receptor blockers have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor blockers should be closely observed for hypotension.

Amlodipine:
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section Toxicology).

Lactation:
Telmisartan + Amlodipine besilate (TWYNSTA) is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Non-clinical studies have shown excretion of telmisartan in breast milk. Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. Because of the potential adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of this therapy for the mother (see section Contraindications).

Fertility:
No studies on fertility in humans with the fixed dose combination or with the individual components have been performed.

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.

In non-clinical studies, no effects of telmisartan on male and female fertility were observed.

In some patients treated by calcium channel blockers, reversible biochemical changes in the head of spermatozoa have been reported.
Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section Toxicology).

Driving and Using machines
No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that syncope, somnolence, dizziness, or vertigo may occasionally occur when taking antihypertensive therapy.
If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Interactions
No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions linked to the combination
No drugs interaction studies have been performed with Telmisartan + Amlodipine besilate (TWYNSTA) and other medicinal products

Other antihypertensive agents
The blood pressure lowering effect of Telmisartan + Amlodipine besilate (TWYNSTA) can be increased by concomitant use of other antihypertensive medicinal products.

Agents with blood pressure lowering potential
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Telmisartan + Amlodipine besilate (TWYNSTA), e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan
Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.
Cases have also been reported with angiotensin II receptor blockers including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with NSAIDs (i.e. ASA at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and their renal function should be monitored at the beginning of combined treatment.
A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Interactions linked to amlodipine

Grapefruit and grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers
Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine
No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% -40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Simvastatin
Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77% compared to simvastatin alone. Therefore, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Additional information
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Adverse Reactions
Summary of the safety profile
The safety and tolerability of Telmisartan + Amlodipine besilate (TWYNSTA) has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

No additional adverse reactions were identified in clinical trials with the combination telmisartan plus amlodipine compared to the adverse reactions of the monocomponents. Peripheral oedema, a recognised dose dependent adverse reaction of the monocomponent amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

Adverse reactions previously reported with one of the monocomponents (telmisartan or amlodipine) may be potential adverse reactions with Telmisartan + Amlodipine besilate (TWYNSTA) as well, even if not observed in clinical trials or during the post-marketing period. Therefore in addition to the reported adverse reactions during the Telmisartan + Amlodipine besilate (TWYNSTA) development programme all adverse reactions reported in patients who received telmisartan or amlodipine monotherapy, have been listed for Telmisartan + Amlodipine besilate (TWYNSTA).

Tabulated summary of adverse reactions
The following adverse reactions derived from the use of the telmisartan/amlodipine combination or the use of the monocomponents (telmisartan or amlodipine) in clinical trials or from post-marketing experience are shown in the table below classified by MedDRA System organ class and MedDRA Preferred terms.

MedDRA System Organ Class terminology	Adverse reactions
Infections and infestations	sepsis (including fatal outcome)[2]
	upper respiratory tract infection [2]
	urinary tract infection [2]
	cystitis [1,2]
Blood and lymphatic system disorders	leukopenia [3]
	thrombocytopenia [2,3]
	anaemia [2]
	eosinophilia [2]
Immune system disorders	anaphylactic reaction [2]
	hypersensitivity [2,3]
Metabolism and nutrition disorders	hyperkalaemia [2]
	hypoglycaemia (in diabetic patients) [2]
	hyperglycaemia [3]
	hyponatraemia [2]
Psychiatric disorders	depression [1,2,3]
	anxiety [1,2,3]
	confusional state [3]
	insomnia [1,2,3]
	mood altered [3]

MedDRA System Organ Class terminology	Adverse reactions
Nervous system disorders	syncope (faint) [1,2,3]
	somnolence [1,3]
	dizziness [1,3]
	extrapyramidal disorder [3]
	hypertonia [3]
	migraine [3]
	headache [1,3]
	neuropathy peripheral [1,3]
	paraesthesia [1,3]
	hypoaesthesia [1,3]
	dysgeusia [1,3]
	tremor [1,3]
Eye disorders	visual impairment [2,3]
	diplopia [3]
Ear and labyrinth disorders	vertigo [1,2]
	tinnitus [3]
Cardiac disorders	myocardial infarction [3]
	ventricular tachycardia [3]
	arrhythmia [3]
	atrial fibrillation [3]
	bradycardia [1,2,3]
	tachycardia [2]
	palpitations [1,3]
Vascular disorders	hypotension [1,2,3]
	orthostatic hypotension [1,2]
	flushing [1,3] vasculitis [3]
Respiratory, thoracic and mediastinal disorders	dyspnoea [2,3]
	cough [1,3]
	rhinitis [3]
Gastrointestinal disorders	pancreatitis [3]
	gastritis [3]
	abdominal pain [1,2,3]
	diarrhoea [1,2,3]
	vomiting [1,2,3]
	gingival hypertrophy [1,3]
	dyspepsia [1,2,3]
	constipation [3]
	nausea [1,3]
	dry mouth [1,2,3]
	flatulence [2]
	abdominal discomfort [2]
	change of bowel habit [3]
Hepatobiliary disorders	hepatitis [3]
	jaundice [3]
	hepatic function abnormal/ liver disorder [2] Most cases of hepatic function abnormal/ liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.
	hepatic enzyme increased (mostly consistent with cholestasis) [3]
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis [3]
	Stevens-Johnson syndrome [3]
	angioedema (including fatal outcome) [2,3]
	erythema multiforme [3]
	dermatitis exfoliative [3]
	drug eruption [2]
	toxic skin eruption [2]
	photosensitivity reaction [3]
	urticaria [2,3]
	eczema [1,2]
	erythema [1,2]
	rash [1,2,3]
	pruritus [1,2,3]
	alopecia [3]
	purpura [3]
	skin discolouration [3]
	hyperhidrosis [2,3]

MedDRA System Organ Class terminology	Adverse reactions
Musculoskeletal and connective tissue disorders	**arthralgia** [1,2,3]
	back pain [1,2,3]
	pain in extremity (leg pain) [1,2]
	tendon pain (tendonitis like symptoms) [2]
	joint swelling [3]
	muscle spasms (cramps in legs) [1,2,3]
	myalgia [1,2,3]
Renal and urinary disorders	**renal impairment (including acute kidney injury)** [2]
	nocturia [1,3]
	micturition disorder [3]
	pollakiuria [3]
Reproductive system and breast disorders	**erectile dysfunction** [1,3]
	gynaecomastia [3]
General disorders and administration site conditions	**chest pain** [1,2,3]
	pain [3]
	oedema [1,3]
	oedema peripheral [1]
	asthenia (weakness) [1,2,3]
	fatigue [1,3]
	malaise [1,3]
	influenza like illness [2]
Investigations	**hepatic enzyme increased** [1,2]
	blood creatinine increased [2]
	blood creatine phosphokinase increased [2]
	haemoglobin decreased [2]
	blood uric acid increased [1,2]
	weight increased [3]
	weight decreased [3]

1 Adverse reactions of FDC telmisartan+amlodipine
2 Adverse reactions of telmisartan as monotherapy
3 Adverse reactions of amlodipine as monotherapy

Overdose

Symptoms

There is no experience of overdose with Telmisartan + Amlodipine besilate (TWYNSTA). Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.
The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia also occurred.
Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome may occur.

Therapy

If symptomatic hypotension should occur, supportive treatment should be instituted.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

Pharmacological properties

Pharmacotherapeutic group: angiotensin II receptor blocker, plain (telmisartan), combinations with dihydropyridine derivatives (amlodipine)

ATC Code: C09DB04

Mode of action

Telmisartan + Amlodipine besilate (TWYNSTA) combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor blocker, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Telmisartan + Amlodipine besilate (TWYNSTA) once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan:

Telmisartan is an orally effective and specific angiotensin II receptor (type AT1) blocker. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long lasting.

Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan.
Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

In man, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Amlodipine:

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion blocker) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non- dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

Pharmacodynamics

Telmisartan

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies.

There is an apparent trend to a dose relationship to a time to recovery of baseline SBP. In this respect data concerning DBP are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan). Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension. Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy.

Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Amlodipine

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Clinical Trials

Telmisartan

Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older

with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of cardiovascular high risk patients.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years. The population studied was 73 % male, 74 % Caucasian, 14 % Asian and 43 % were 65 years of age or older. Hypertension was present in nearly 83 % of randomized patients; 69 % of patients had a history of hypertension at randomization and an additional 14 % had actual blood pressure readings above 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76 %), statins (62 %), beta-blockers (57 %), calcium channel blockers (34 %), nitrates (29 %) and diuretics (28 %).

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure.

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Telmisartan had similar efficacy to ramipril in reducing the primary endpoint. The incidence of the primary endpoint was similar in the telmisartan (16.7 %), ramipril (16.5 %) and telmisartan plus ramipril combination (16.3 %) arms. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019). The treatment effect was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint based on age, gender, race, baseline therapies or underlying disease.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo. The hazard ratio of telmisartan vs. ramipril for this endpoint in ONTARGET was 0.99 (97.5 % CI 0.90 - 1.08, p (non-inferiority) = 0.0004).

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore, the use of a combination of telmisartan and ramipril is not recommended in this population.

Amlodipine:
Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in Patients with Heart Failure:
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Fixed dose combination (Telmisartan + Amlodipine besilate (TWYNSTA)):
In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥95 and <110 mmHg) underwent a 3-4 week placebo run-in period in order to wash out all antihypertensive medications before they were randomised to a double-blind active treatment. Treatment with each combination dose of Telmisartan + Amlodipine besilate (TWYNSTA) resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

The telmisartan/amlodipine combinations showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range:

mmHg reduction	Telmisartan + Amlodipine besilate (TWYNSTA) dose
-21.8/-16.5	40/5 mg
-22.1/-18.2	80/5 mg
-24.7/-20.2	40/10 mg
-26.4/-20.1	80/10 mg

The proportions of patients reaching a diastolic blood pressure <90 mmHg with a telmisartan/amlodipine combination were:

%	Telmisartan + Amlodipine besilate (TWYNSTA) dose
71.6	40/5 mg
74.8	80/5 mg
82.1	40/10 mg
85.3	80/10 mg

A subset of 1050 patients in the factorial design study had moderate to severe hypertension (DBP ≥100 mmHg). In these patients who are likely to need more than one antihypertensive agent to achieve blood pressure goal, the observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (-22.2/-17.2 mmHg with 40/5 mg; -22.5/-19.1 mmHg with 80/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (-21.0/-17.6 mmHg). Additionally, combination therapy showed notably lower oedema rates (1.4% with 40/5 mg; 0.5% with 80/5 mg; 17.6% with amlodipine 10 mg).
The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, double-blind, active-controlled study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received Telmisartan + Amlodipine besilate (TWYNSTA) (40/5 mg or 80/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combination was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures:

mmHg reduction	dose
-13.6/-9.4	Telmisartan + Amlodipine besilate (TWYNSTA) 40/5 mg
-15.0/-10.6	Telmisartan + Amlodipine besilate (TWYNSTA) 80/5 mg
-6.2/-5.7	amlodipine 5 mg
-11.1/-8.0	amlodipine 10 mg

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were 56.7% with Telmisartan + Amlodipine besilate (TWYNSTA) 40/5 mg and 63.8% with Telmisartan + Amlodipine besilate (TWYNSTA) 80/5 mg compared to 42.0% with amlodipine 5 mg and 56.7% with amlodipine 10 mg.

Oedema related events (peripheral oedema, generalised oedema, and oedema) were significantly lower in patients who received Telmisartan + Amlodipine besilate (TWYNSTA) (40/5 mg or 80/5 mg) as compared to patients who received amlodipine 10 mg (4.4% vs. 24.9%, respectively).

In another multicentre, double-blind, active-controlled study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received Telmisartan + Amlodipine besilate (TWYNSTA) (40/10 mg or 80/10 mg) or amlodipine alone (10 mg). After 8 weeks, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressures:

mmHg reduction	dose
-11.1/-9.2	Telmisartan + Amlodipine besilate (TWYNSTA) 40/10 mg
-11.3/ -9.3	Telmisartan + Amlodipine besilate (TWYNSTA) 80/10 mg
-7.4/-6.5	amlodipine10 mg

The proportions of patients with normalisation of blood pressure (trough seated diastolic blood pressure <90 mmHg at the end of the trial) were 63.7% with Telmisartan + Amlodipine besilate (TWYNSTA) 40/10 mg and 66.5% with Telmisartan + Amlodipine besilate (TWYNSTA) 80/10 mg compared to 51.1% with amlodipine 10 mg.

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of Telmisartan + Amlodipine besilate (TWYNSTA) was maintained over the trial period.

In patients not adequately controlled on amlodipine 5 mg, Telmisartan + Amlodipine besilate (TWYNSTA) achieved similar (40/5 mg) or better (80/5mg) blood pressure control compared to amlodipine 10 mg with significantly less oedema.
In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, Telmisartan + Amlodipine besilate (TWYNSTA) 40/5 mg or 80/5 mg may achieve similar blood pressure control with less oedema.
The antihypertensive effect of Telmisartan + Amlodipine besilate (TWYNSTA) was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Telmisartan + Amlodipine besilate (TWYNSTA) has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25.620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Pharmacokinetics

Pharmacokinetics of the Fixed Dose Combination
The rate and extent of absorption of Telmisartan + Amlodipine besilate (TWYNSTA) are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetic of the single components
Absorption
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50%. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food.
The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
Telmisartan is largely bound to plasma protein (> 99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vss) is approximately 500 L.

The volume of distribution of amlodipine is approximately 21 L/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

Biotransformation
Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Amlodipine is extensively (approximatively 90%) metabolised by the liver to inactive metabolites.

Elimination
Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, exclusively as unchanged compound. Cumulative urinary excretion is < 2% of dose. Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min compared with hepatic blood flow (about 1500 mL/min).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Linearity
The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan.

PK in specific populations

Paediatric population (age below 18 years)
No pharmacokinetic data for Telmisartan + Amlodipine besilate (TWYNSTA) are available in the paediatric population.

Gender differences
Gender differences in plasma concentrations of telmisartan were observed, C_{max}, and AUC being approximately 3-and 2-fold higher, respectively, in females compared to males without relevant influence on efficacy.

Geriatric patients
The pharmacokinetics of telmisartan do not differ between younger and geriatric patients. Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life.

Renal impairment
Lower plasma concentrations of telmisartan were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100%. The elimination half-life is not changed in patients with hepatic impairment.

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC.

Toxicology
Since the non-clinical toxicity profiles of telmisartan and amlodipine besilate are not overlapping, no exacerbation of toxicity was expected for the combination.

This has been shown in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine besilate were tested. In this study no additive or greater than additive adverse effects of amlodipine and telmisartan in combination as well as no change of the toxicity profile with regard to target organs were observed.

With respect to Telmisartan + Amlodipine besilate (TWYNSTA), separate reproductive toxicity studies assessing the potential effects of telmisartan and amlodipine on male and female fertility when both compounds are given in combination, have not been conducted.
Non-clinical data available for the components of this fixed dose combination are reported below.

Telmisartan
In non-clinical safety studies doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit) and changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically mediated side effects, known from non- clinical studies with both angiotensin converting enzyme inhibitors and angiotensin II blockers, were prevented by oral saline supplementation.

In both species increased plasma renin activity and hypertrophy/ hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of ACE- inhibitors and other angiotensin II blocker, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed; at toxic doses levels, however, non-clinical studies indicated some hazardous potential of telmisartan to foetal development (increased number of late resorptions in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality.

No effects of telmisartan on male and female fertility were observed.

There was no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice.

Amlodipine
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 8 times* the MRHD of 10 mg/day on a mg/m^2 basis.
In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg.

Availability

Tablets of 40/5 mg	Alu/Alu blister pack of 10's (Box of 30's)
Tablets of 40/10 mg	Alu/Alu blister pack of 10's (Box of 30's)
Tablets of 80/5 mg	Alu/Alu blister pack of 10's (Box of 30's)
Tablets of 80/10 mg	Alu/Alu blister pack of 10's (Box of 30's)

Store in a safe place out o

Caution
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

Store at temperatures not exceeding 30°C.
Store in the original package in order to protect from light and moisture.

IMPORTANT: Moisture sensitive tablets – do not remove from blisters until immediately before administration.

For any suspected adverse drug reaction, please seek medical attention immediately. Report this to the FDA: www.fda.gov.ph and email us at PV_local_Philippines@boehringer-ingelheim.com.

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*T.M. Reg. Phil. Pat. Off.

DRP-7255 (40 mg/5 mg Tablet)
DRP-7256 (40 mg/10 mg Tablet)
DRP-7254 (80 mg/5 mg Tablet)
DRP-7443 (80 mg/10 mg Tablet)

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of the reach of children!